Remarks

I. Status of the Claims

Claims 84-122 and 127-131 are pending in the application, with claims 84 and 127 being the independent claims. Claims 123-126 were previously canceled without prejudice. Applicants reserve the right to pursue the canceled subject matter in related applications. Claims 98, 100-102, and 104-106 have been withdrawn from consideration by the Examiner as reading solely on non-elected species, but remain pending. Claim 90 has been amended. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

II. The Amendments

Claim 90 is amended to correct a clear spelling error. Accordingly, no new matter is believed to have been added by the amendments, and their entry is respectfully requested.

III. Brief Description of the Invention

The present invention is directed to a method of selecting polynucleotides which encode an antigen-specific human immunoglobulin molecule by expressing vaccinia virus libraries of immunoglobulin heavy and light chains in mammalian host cells.

The present invention provides for the direct selection of high-affinity fully human antibodies, which result in a lower chance of immune rejection of therapeutics than may be the case for humanized or murine antibodies. In addition, the selected

antibodies do not have to be re-engineered as for use as full immunoglobulins as do the fragments isolated from phage display, since the claimed invention provides for direct expression and selection of complete antibodies. The present invention further provides the ability to achieve extremely high levels of combinatorial diversity of immunoglobulin heavy and light chains which results in an increased likelihood of identifying antibodies with high-affinity, high specificity, and desired function.

The invention also allows for the direct selection of antibodies that would otherwise be difficult or impossible to identify with other antibody selection systems. For example, production of human antibodies in transgenic mice that have been genetically engineered to express human immunoglobulin genes, besides being time consuming and costly, is limited by a problem known as "tolerance." Most important human genes have a mouse homolog that may be as much as 90% homologous at the protein level. When the mouse produces antibodies to the human protein, they may be biased toward recognizing eptiopes that are different between the human and mouse (*i.e.*, the mouse will not produce antibodies to epitopes found in its own proteins). However, these may not be the optimal target epitopes. In another example, phage display is not generally suitable for use in screening for antibodies for membrane-associated proteins that are difficult to purify (*e.g.*, multi-pass membrane receptors), and which must therefore be screened using whole cells or fragments, because phage particles have non-specific interactions with mammalian cells and thereby interfere with the antibody screening process.

Thus, the present invention provides numerous important and distinct advantages over the previously available antibody selection technologies such as phage display and transgenic mice.

IV. The Rejections

A. Rejections under 35 U.S.C. § 103

Claims 84, 88-97, 99, 103, 107-122, and 127-131 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rowlands *et al.*, WO 93/01296 (hereinafter "Rowlands"), Zauderer, WO 00/28016 (hereinafter "Zauderer"), and Waterhouse *et al.*, *Nuc. Acids Res.* 21: 2265-66 (1993) (hereinafter "Waterhouse") (collectively referred to herein as "the cited references"). Office Action dated April 21, 2006 ("Office Action"), at page 3. Applicants respectfully traverse this rejection.

In particular, the Examiner asserts that one of ordinary skill in the art would have been motivated to make libraries as taught by Zauderer with heavy and light chain antibodies as disclosed in Rowlands, and a reasonable expectation of success, because both references discuss the use of vaccinia virus vectors in mammalian cells. *Id.* at page 3 and pages 9-10. The Examiner further asserts that there was a motivation to combine the cited references and a reasonable expectation of success because "Waterhouse et al. teach that 'associated' light and heavy chains are a 'preferred' embodiment for screening and/or affinity maturation because they can be 'simultaneously co-selected'. . .which would encompass the 'associated' heavy/light chains described by Rowlands et al.," and that Waterhouse *et al.* teach producing two libraries simultaneously. *Id.* at 9 (internal citations omitted). Finally, the Examiner states that "Rowlands et al. state that the use of

vaccinia virus as vectors is well known and has wide applications and explicitly state that it can be used for antibody production." *Id.*

Applicants respectfully submit that, for the reasons discussed in their previously-filed replies (of record, each of which is incorporated herein by reference in its entirety), as well as the reasons set forth below, that the present invention is not obvious over Rowlands in view of Zauderer and Waterhouse.

1. The Office Has Not Established a Prima Facie *Case of Obviousness*

Applicants respectfully submit that the Office has not established a *prima facie* case of obviousness in the present case.

Three basic criteria must be met to establish a *prima facie* showing of obviousness:

> First, there must be some suggestion or motivation, whether in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference. . . must teach or suggest all the claim limitations.

Manual of Patent Examining Procedure (M.P.E.P.) § 2143 (Rev 3, Aug. 2005) at 2100-135. "The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure." *Id.*

Furthermore, the following tenets of patent law must be followed when applying 35 U.S.C. § 103:

(A) The claimed invention must be considered as a whole;

> (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; [and]
>
> (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; ...

M.P.E.P. § 2141 at 2100-125 (citing *Hodosh v. Block Drug Co., Inc.* 786 F.2d 1136, 1143 n.5 (Fed. Cir. 1986)).

Applicants respectfully maintain that the Office has not made a *prima facie* showing of obviousness because there was no reasonable expectation of success in combining the cited references, there was not even a motivation to combine the cited references, and the cited references do not teach every element of the claimed invention. Furthermore, the Office has not considered the claimed invention as a whole, has not considered the references as a whole, and has used impermissible hindsight based on Applicants' own disclosure to selectively piece together the elements of the claimed invention from the cited references.

a. There Was No Reasonable Expectation of Success in Combining the Cited References

Applicants respectfully maintain that one of ordinary skill in the art would not have had a reasonable expectation of success in combining Rowlands with Zauderer and Waterhouse to arrive at the claimed invention.

Rowlands discloses the expression of a single immunoglobulin heavy chain and a single immunoglobulin light chain (*i.e.*, of the humanized Campath 1 antibody) in vaccinia virus vectors. Zauderer discloses introduction of one vaccinia virus expression library for screening tumor antigens. Waterhouse discloses the expression of heavy and light chain fragments in a combinatorial phage display library in prokaryotic cells.

The Examiner asserts that, because "Rowlands et al teach a method for producing antibodies in vaccinia infected 'mammalian' cells," that "the conclusion that a person of skill in the art would know how to express an antibody in a 'mammalian' cell is reasonable." Office Action at 27. The Examiner further asserts that because "Zauderer et al teach how to make and/or use a library of proteins using a vaccinia virus vector like the vaccinia virus vector disclosed by Rowlands ... the conclusion that a person of skill in the art would know how to make and/or use a library of proteins, including antibodies, with a vaccinia virus is reasonable." *Id.* (citations omitted). Applicants disagree. Even if it is reasonable to conclude that one of ordinary skill in the art would know in view of Rowlands how to express an antibody, and would know in view of Zauderer how to make and use a vaccinia virus expression library, it does not follow that the artisan could, with a reasonable expectation of success, arrive at a method of selecting polynucleotides encoding antigen-specific immunoglobulins by introducing two libraries of vaccinia virus vectors into mammalian host cells.

This gap in logic is highlighted by the Storkus Declaration, filed on July 21, 2005, wherein Dr. Storkus indicated that the expression of a single antibody as in Rowlands is far simpler than expression of pairs of immunoglobulin chains from two separate libraries, and that assembling separate chains from two libraries is a different concern than expressing one library as in Zauderer. Storkus Declaration at page 5. The Examiner points to statements in Zauderer that indicate that it was possible for the first time to efficiently construct DNA libraries in vaccinia virus-derived vectors as support that one of ordinary skill in the art would have a reasonable expectation of success in combining Zauderer with Rowlands. Office Action at page 27 (citing Zauderer at page

15, paragraph 1; page 22, last two paragraphs, and Example 6). Applicants agree that Zauderer does not state that tri-molecular recombination should be limited to expressing "everything but antibodies." *See* Office Action at page 27. But the fact that Zauderer does not say that the disclosed libraries cannot be used for expressing immunoglobulins is not the same as the reference affirmatively saying that such libraries can be used for expressing immunoglobulins. By the Examiner's reasoning, any reference that does not explicitly exclude or disclaim a particular feature could be said to teach that feature (*i.e.*, if "X" is not explicitly disclaimed in the reference, then the reference teaches "X"). This logic is not correct. A *prima facie* showing of obviousness requires that the cited references teach every element of the claimed invention; it is not sufficient to merely show that the references do not expressly exclude a particular element. Thus, not only was there no reasonable expectation of success in combining Rowlands and Zauderer, as discussed in greater detail, *infra*, the cited references do not even teach every element of the claimed invention.

Furthermore, the logical gap is not filled by the citation of Waterhouse. Despite the statement at page 28 of the Office Action that "[t]he Examiner has never contended that the eukaryotic systems should somehow employ prokaryotic reaction conditions in some sort of hybrid expression system," the Office has provided no other explanation for how one of ordinary skill in the art could achieve the claimed invention based on the combination of Rowlands with Zauderer and Waterhouse. One of ordinary skill in the art would not have thought that the methods of Waterhouse would be applicable for use in mammalian expression systems. For example, Dr. Storkus indicated that a eukaryotic cell system was thought to be impractical for screening a sufficient number of eukaryotic

cells to find an antibody that had specificity for a specific antigen of interest. Storkus Declaration at page 3. The Examiner even specifically recognized that one of ordinary skill in the art would have thought that "producing high affinity antibodies ... [depends] on the size of the library that can be created with that expression system," and that "[t]his is a general theme in screening because finding the right antibody depends, in part, on producing that antibody and that if that antibody is never produced (i.e., a small library) then it cannot be selected for in the screening assay." Office Action at pages 26-27. Hence, the limits on the ability to screen eukaryotic host cells as opposed to phage particles would have been considered an obstacle to the reasonable expectation of success in arriving at the claimed methods by combining Rowlands with Zauderer and Waterhouse.

Although the Examiner again asserts that "the prokaryotic/eukaryotic distinctions to which Applicants refer. . .are not at issue in this case," Office Action at page 28, Applicants respectfully maintain that, quite to the contrary, these differences are at the heart of the issue of why one of ordinary skill in the art would not have had a reasonable expectation of success in combining Rowlands with Zauderer and Waterhouse. The Examiner's reliance on Waterhouse "to show that the production of two libraries (e.g., heavy and light chain) will lead to more favorable antibodies via a co-selection process regardless of how those antibodies are produced," present Office Action at page 19 (emphasis in original), is improper because: 1) it fails to consider the reference as a whole (*i.e.*, that it discloses the use of heavy and light chain immunoglobulin repertoires in a *prokaryotic* system); and 2) because it focuses on the obviousness of differences and substitutions in the references (*i.e.*, two expression libraries substituted for one,

eukaryotic substituted for prokaryotic), rather than considering the claimed invention as a whole.

Applicants respectfully maintain that the citation of *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991), is relevant to the present case and the fact that the Office has not shown that one of ordinary skill in the art would have had a reasonable expectation of success. *See* Office Action at page 36.

In *Vaeck* the claimed invention was directed to a chimeric gene capable of being expressed in cyanobacteria cells, comprising a promoter region effective for expression of a DNA fragment in Cyanobacterium and at least one DNA fragment from a insecticidally active *Bacillus* bacterial gene. *Vaeck*, 974 F.2d at 488. The Federal Circuit determined that there was no motivation to combine, and no reasonable expectation of success in combining: 1) a reference that disclosed the expression in cyanobacteria of a chimeric gene comprising a chloroplast promoter sequence fused to a CAT selectable marker gene; and 2) three secondary references that collectively disclosed the expression of genes encoding certain *Bacillus* insecticidal genes in three different species of bacterial hosts, two of the genus *Bacillus* and *E. coli*. *Id.* The court determined that "[t]he prior art simply does not disclose or suggest the expression in cyanobacteria of a chimeric gene encoding an insecticidally active protein, or convey to those of ordinary skill in the art a reasonable expectation of success in doing so. . . . The expression of antibiotic resistance-conferring genes in cyanobacteria, without more, does not render obvious the expression of unrelated genes in cyanobacteria for unrelated purposes." *Id.* at 493.

The Examiner attributes the holding in *Vaeck* to the idea that "[a] person of ordinary skill in the art simply wouldn't be able to predict how the cyanobacteria would respond to the introduction of a Bacillus gene given how little was known about these newly classified prokaryotic hosts." Office Action at page 36. The Examiner suggests that the present case is distinguishable from *Vaeck* because "Rowlands et al. state that the use of vaccinia virus as vectors is well known and has wide applicants and explicitly state that it can be used for antibody production." *Id.* at pages 36-37. In particular, the Examiner points to a passage from Rowlands that states "the use of vaccinia virus as a vector for expression of foreign genes has been employed for almost a decade," Office Action at page 37 (quoting Rowland et al., page 4, first full paragraph), and concludes that "*In re Vaeck* provides strong support for the Examiner's position." *Id.* However, the Examiner is disregarding the key fact that Rowlands describes only the expression of a single heavy chain and a single light chain from vaccinia virus vectors. This does not show that one of ordinary skill in the art could predict how infecting a library of heavy chains and a library of light chains into mammalian host cells would work. Therefore, Applicants respectfully maintain that, as in *Vaeck*, one of ordinary skill in the art would not have had a reasonable expectation of success in applying the methods disclosed in Waterhouse to a eukaryotic expression system.

The Office's conclusion that one of ordinary skill in the art would have had a reasonable expectation of success is based on erroneous assumptions. One of ordinary skill in the art would not expect, simply because Waterhouse *et al.* had developed a method of screening antibody fragments from a library of heavy chains and a library of light chains expressed in phage particles, that the same thing could be done with vaccinia

viruses in eukaryotic cells. This is so despite the fact that Rowlands describes how to express a single antibody heavy chain and a single antibody light chain from vaccinia viruses in mammalian cells, and despite the fact that Zauderer describes how to express one vaccinia virus library in mammalian cells. There simply is not sufficient guidance in any of the cited references to indicate how one of ordinary skill in the art could achieve the claimed method with a reasonable expectation of success by combining them. As such, the Office has not established a *prima facie* showing of obviousness.

b. There Was No Motivation to Combine the Cited References

Applicants respectfully maintain that, not only was there no reasonable expectation of success in combining Rowlands with Zauderer and Waterhouse to arrive at the claimed invention, one of ordinary skill in the art would not have *even been motivated* to combine these references. As set forth, *supra*, Rowlands discloses the expression of a single immunoglobulin heavy chain and a single immunoglobulin light chain (*i.e.*, of the humanized Campath 1 antibody) in vaccinia virus vectors. Zauderer discloses the expression of one vaccinia virus library. Waterhouse discloses the expression of heavy and light chain fragments in a combinatorial phage display library in prokaryotic cells. There is no motivation or suggestion in Rowlands that the disclosed method of expressing one antibody should, or even could, be used for a method of screening *libraries* of immunoglobulins and no motivation or suggestion in Zauderer to express libraries of antigen-specific immunoglobulins. Likewise, there is no motivation or suggestion in Waterhouse to introduce two *vaccinia virus* expression libraries encoding *whole* immunoglobulin heavy and light chains into *mammalian cells*. Thus, the

motivation or suggestion to combine the references does not come from any of the cited references or any combination of these references.

In applying 35 U.S.C. § 103, the Office must consider the claimed invention as a whole, and the cited references as a whole. *See* MPEP § 2141 at 2100-125. Applicants respectfully submit that, in concluding that one of ordinary skill in the art would have been motivated to combine the cited references, the Office is not considering either the claimed invention or the references as a whole.

i. The Office is Not Considering the Claimed Invention as a Whole

The Office appears to have distilled the claimed invention down to what it perceives as the "gist" of simply "a method of producing an antibody," and therefore is not properly considering the claimed invention as a whole. *See* M.P.E.P. § 2141.02 at 2100-130 (citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983)).

The Examiner acknowledges that "Rowlands et al. are deficient in that they do not specifically teach the use of a 'library' of first/second polynucleotides," Office Action at page 5, but asserts that Zauderer "teach[es] the use of a library of polynucleotides in a vaccinia virus vector" and that Waterhouse "teach[es] that a 'library can be usefully employed to screen for antibodies with high affinity to various antigens including the use of heavy/light chains that are 'packaged together' i.e., two libraries." *Id.* at page 6 (emphasis in original).

However, in simplifying the characterization of Applicants' invention and the cited references as such, the Examiner has disregarded the claimed invention as a whole. In particular, the Examiner has disregarded the claimed features of introducing *two*

vaccinia virus libraries encoding *whole* immunoglobulin heavy and light chains into *mammalian host cells*. Rather, as discussed in detail below, these features of the claimed invention have been selectively plucked from the cited references and pieced together by the Examiner to assert that the claimed invention is obvious. This is an improper evaluation of the invention under 35 U.S.C. § 103.

ii. The Office is not Properly Considering the Waterhouse Reference as a Whole

"'It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.'" *In re Hedges*, 783 F.2d 1038, 1041, 228 U.S.P.Q. 685 (Fed. Cir. 1986) (quoting *In re Wesslau*, 353 F.2d 238, 241 147, U.S.P.Q. 391, 393 (CCPA 1965)) (underline in original).

Applicants respectfully re-emphasize the point that Waterhouse discloses co-selection of heavy and light chain antibody *fragments* that are expressed as *phage* fusion proteins in *prokaryotic host cells*. One of ordinary skill in the art would look to all of these aspects of Waterhouse in determining whether the method of selecting a polynucleotide encoding an immunoglobulin fragment from the phage display libraries described therein could be performed in a vaccinia virus system. There is no teaching or suggestion in Waterhouse that their method of introducing phage libraries into prokaryotic cells could be used for introducing vaccinia virus vectors into mammalian host cells. Applicants respectfully assert that the Office's characterization of the teachings of Waterhouse, both explicit and implied, is incorrect.

In particular, the Examiner asserts that this substitution would have been obvious because Waterhouse, "when taken as a whole, impliedly teaches the advantages of using co-selection to produce more favorable antibodies 'regardless' of the method of production." *Id.* at page 26. The Examiner further asserts that "producing high affinity antibodies does not depend on the phage expression system but, rather, on the size of the library that can be created with that expression system," and concludes that the benefits of increased library size, increased library diversity, and presentation of both VH and VL chains to the antigen "are not going to change when the expression system is altered from prokaryotic to eukaryotic because ... these benefits are independent of the expression system. *Id.* at pages 26-27 (citations omitted). Applicants disagree.

To the contrary, the benefits that the Examiner indicates are implied by Waterhouse *were* thought to be dependent on the type of expression system. For example, Dr. Storkus stated that he did not think it would "be practical to screen the number of eukaryotic cells necessary in order to find an antibody that had specificity for a specific antigen of interest." Storkus Declaration at page 3. In particular, Dr. Storkus stated that "the throughput for screening phage exceeded the expected throughput for screening libraries expressed in eukaryotic cells by as much as four orders of magnitude," and that "antibody fragments expressed in phage ... are assembled in the periplasmic space [of the prokaryotic host cell]. The conditions of assembly in the eukaryotic cytoplasm are far different from those that apply in the periplasmic space and it could not be known what effect this would have on antibody assembly." *Id.* at pages 3-4. Thus, the size of the library that could be screened and the characteristics of heavy and light chain assembly were thought to be dependent on whether the expression system

was prokaryotic (*e.g.*, bacterial) or eukaryotic (*e.g.*, mammalian). When properly considering how Waterhouse would be viewed by one of ordinary skill in the art, the reference actually teaches away from the claimed invention because it emphasizes features that one of ordinary skill in the art would not have associated with eukaryotic expression systems (*e.g.*, ability to generate and screen large libraries and packaging of heavy and light chains together in the same phage particle).

In any event, nowhere does Waterhouse teach or fairly suggest how to apply its teachings to a method of expressing a single heavy and light chain as in Rowlands and/or a method of expressing one vaccinia virus library as in Zauderer. *See, In re Bell*, 991 F.2d 781,785 (Fed. Cir. 1993). Therefore, one of ordinary skill in the art would not have been motivated to combine the cited references, and the Office has failed to establish a *prima facie* showing that the claimed invention was obvious.

iii. The Office is Focusing on the Obviousness of Differences and Substitutions

Applicants respectfully maintain that the Office is impermissibly focusing on the obviousness of differences and substitutions between the claimed invention and the cited references to establish a *prima facie* case of obviousness, and that, contrary to the Examiner's arguments, *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986), is relevant to the present case. *See* Office Action at page 28.

In *Hybritech*, the Federal Circuit held that a patent claiming a sandwich-type immunoassay that used *monoclonal* antibodies was not obvious in view of prior art references that disclosed sandwich assays using *polyclonal* antibodies, even in view of references that disclosed monoclonal antibody production and the use of a single monoclonal antibody in a competitive immunoassay. *Id.* at 1380-81. The Examiner

argues that, in *Hybritech*, "[t]he claims were upheld, in part, because four of the most important references that were used to invalidate these claims in the district court, according to the CAFC, did not constitute prior art." Office Action at page 28 (citing *Hybritech*, 802 F.2d at 1380. The Examiner further states that "According to Judge Rich, none of the remaining articles suggested the use of monoclonal antibodies in sandwich assays" *Id.* at page 29. This is irrelevant to the point Applicants are making in reference to *Hybritech*. The Federal Circuit concluded that "[f]ocusing on the obviousness of substitutions and differences instead of on the invention as a whole as the district court did in frequently describing the claimed invention as *the mere substitution of monoclonal for polyclonal antibodies in a sandwich assay*, was a legally improper way to simplify the difficult determination of obviousness." *Hybritech*, 802 F.2d at 1383 (emphasis added).

It is in that respect that the present case is analogous to *Hybritech*. Namely, in the present case, the Examiner is focusing on the notion that features of the method for selecting antibody fragments from a prokaryotic phage library expression system, as disclosed in Waterhouse, can merely be substituted into the method of expressing a single antibody heavy and light from vaccinia virus vectors as in Rowlands and/or the expression of one vaccinia virus library as in Zauderer to arrive at the present claimed methods. As established in *Hybritech*, this type of simple substitution of elements is an improper analysis for establishing a *prima facie* case of obviousness.

iii. "Obvious to Try" is Not the Proper Standard for Determining Obviousness

At the very most, the combination of Rowlands, Zauderer and Waterhouse might be an *invitation to try* selecting polynucleotides encoding an antigen-specific

immunoglobulin molecule or fragment thereof in eukaryotic cells as in the present invention, "but [the cited references] do not suggest how that end might be accomplished." *See e.g., Hybritech* 802 F.2d at 1380. Furthermore, it is well established that "obvious to try" is not the standard for establishing a *prima facie* case of obviousness under 35 U.S.C. § 103. *See e.g., id.*

The Office asserts that "[a]n invention is obvious to try where the prior art provides either no indication of which parameters would be critical or no direction as to which of many possible choices is likely to be successful." Office Action at page 37 (citing *Merck & Co. v. Biocraft Labs, Inc.* 874 F.2d 804, 807 (Fed. Cir.), *cert. denied*, 493, U.S. 975 (1989). According to the Examiner, the present case "is not a situation where there are a large number of possibilities with no expectation of success." *Id.* In particular, the Examiner asserts that one of ordinary skill in the art "would know which parameters are critical to express an antibody in a eukaryotic cell" because Rowlands et al state that the use of vaccinia virus as vectors is well known and has wide applications and explicitly state that it can be used for antibody production. *Id.* The Examiner further asserts that "one of ordinary skill in the art would also know which parameters are critical to form a library in eukaryotic cells," because "Zauderer provides a facile method for expressing libraries using the same vaccinia virus that is presented in Rowlands et al." *Id.* at pages 37-38. Applicants disagree with this assessment.

Even if, as the Office asserts, one of ordinary skill in the art would know which parameters are critical to express an antibody in a eukaryotic cell based on Rowlands, and which parameters are critical to form a library in eukaryotic cells based on Zauderer, one of ordinary skill of art would not know what parameters are critical to express two

libraries in eukaryotic cells and select from them polynucleotides encoding antigen-specific immunoglobulin molecules. Therefore, the claimed invention is not *prima facie* obvious in view of the cited references.

c. The Cited References Do Not Teach Every Element of the Claimed Invention

Applicants respectfully maintain that, in addition to the lack of motivation to combine the cited references, and the lack of a reasonable expectation of success in doing so Rowlands, Zauderer, and Waterhouse does not teach or suggest all of the elements of the claimed invention.

The Examiner cites Rowlands as teaching the expression of separate heavy and light chains that can combine to form a functional antibody from vaccinia virus vectors in mammalian cells. Office Action at page 4. The Examiner cites Zauderer as teaching the use of *one* expression library of polynucleotides constructed in vaccinia virus vectors in mammalian cells. *Id.* at page 6. Waterhouse is cited by the Examiner as teaching the screening of a combinatorial phage library that is generated from a library of light chains and a library of heavy chains that are packaged together in phage particles. *Id.*

As acknowledged by the Examiner, Rowlands does not teach the use of first or second *libraries* of polynucleotides. *Id.* at page 5. Furthermore, Zauderer does not teach or suggest using two expression libraries or immunoglobulin expression libraries.

However, Applicants maintain that this combination of references does not teach or suggest all of the elements of the claimed invention because they do not teach or suggest the introduction of two libraries of polynucleotides constructed in vaccinia virus vectors into eukaryotic cells. The introduction and screening of two libraries of vaccinia virus vectors into eukaryotic cells is a different method than introducing a single vector

encoding a heavy chain and a single vector encoding a light chain as in Rowlands and/or expressing one library as in Zauderer.

The Examiner suggests that the use of two libraries, a heavy chain library and a light chain library, in a eukaryotic system could be inferred by one of ordinary skill in the art from the teachings of Waterhouse. Office Action at page 18. The Examiner also asserts that one of ordinary skill in the art would look to all the relevant papers dealing with phage display because "the advantages associated with being able to select these heavy and light chains in order to produce, for example, antibodies with high affinity, are just as applicable to mammalian expression systems as they are in phage display. The products in each case (i.e. antibodies or antibody libraries) would be the same." *Id.* Applicants disagree.

First, as discussed, *supra*, the Examiner has impermissibly distilled the invention down to what it sees as its "gist": production of an antibody (or antibody library). Then, the Examiner has looked for elements of this "gist" of the invention to establish a *prima facie* showing of obviousness. This is not a proper analysis under 35 U.S.C. § 103. In showing that the cited references teach or suggest each element of the claimed invention, just as with finding a motivation to combine the references, discussed, *supra*, the Office must consider the claimed invention as a whole. When considering the invention as a whole, it is clear that the combination of cited references does not teach or suggest the introduction of two libraries of polynucleotides constructed in separate vaccinia virus libraries into mammalian host cells as in the claimed method.

Second, contrary to the Examiner's assertions, the antibodies and antibody libraries produced by phage display would not necessarily be the same as those produced

by the claimed invention. *See* Office Action at page 19. As noted by the present specification, the phage display strategy "requires that complementarity determining regions (CDRs) of the expressed immunoglobulin fragment be synthesized and fold properly in bacterial cells. Many antigen binding regions, however, are difficult to assemble correctly as a fusion protein in bacterial cells. In addition, the protein will not undergo normal eukaryotic post-translational modifications. As a result, [the phage display] method imposes a different selective filter on the antibody specificities that can be obtained." Specification at page 4.

In view of the foregoing reasons, the Office has not shown that the combination of cited references teaches all of the elements of the claimed invention. Therefore, there has been no *prima facie* showing of obviousness.

d. The Office is Using Impermissible Hindsight to Piece Together the Invention from the Cited References

Although the Examiner points to Rowlands, Zauderer and Waterhouse as supplying all of the elements of the present invention, a point with which Applicants respectfully disagree, this is not sufficient for establishing a *prima facie* case of obviousness under 35 U.S.C. § 103. "[R]ejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be 'an illogical and inappropriate process by which to determine patentability.'" *In re Rouffet*, 149 F.3d 1350, 1375 47 U.S.P.Q.2d 1453 (Fed. Cir. 1998) (quoting *Sensonics, Inc. v. Aerosonic Corp.* 81 F.3d 1566, 1570, 38 U.S.P.Q.2d 1551, 1554 (Fed. Cir. 1996). *See also, In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988) ("One cannot use

hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.").

In asserting that the cited references disclose each and every element of the claimed invention, the Office has used the Applicants' claimed invention itself as a guide to pick out bits of the claimed invention from the cited references without providing a satisfactory showing that one of ordinary skill in the art would have been motivated to combine the cited references or would have had a reasonable expectation of success in the absence of hindsight. It is not sufficient to show that both Zauderer and Rowlands disclose uses of vaccinia virus vectors, especially since the vectors are used for different purposes in each reference and Zauderer does not teach or suggest screening a library of immunoglobulins or, indeed, using two such libraries. Likewise, it is not sufficient to show that Rowlands and Waterhouse both deal with antibodies, especially considering that Rowlands describes a method of expressing a single antibody in a mammalian cell and Waterhouse describes screening a phage library of antibody fragments expressed in prokaryotic cells.

In the previous reply, Applicants discussed the pertinence of *In re Fine* to the present case regarding the use of impermissible hindsight to reconstruct the claimed invention. See Reply filed February 2, 2006, at pages 24-26. The Examiner asserts that the present case is distinguishable from *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988), because *Fine* "provides an example of a 'teaching away' by disclosing that the presence of a claimed element, nitrogen, is undesirable." Office Action at page 25. The Examiner contends that there is no such "teaching away" in the cited references in the present case, and that one of ordinary skill in the art, therefore, would have been motivated to combine

the references. *Id.* at pages 25-26 (citations omitted). However, Applicants respectfully maintain that *Fine* is relevant to the present case in showing that the Office used impermissible hindsight to reconstruct the claimed invention.

In *Fine*, the applicants' claims to a system for detecting and measuring minute quantities of nitrogen-containing compounds were rejected as obvious over the combination of the Eads and Warnick references. *Fine*, 837 F.2d at 1073. Warnick described a means for detecting the concentration of nitric oxide in a sample. *Id.* The teachings of the Eads reference were limited to overcoming the problem of obtaining precise measurements of sulfur compounds. *Id.* at 1074. The Examiner concluded and the Board affirmed that "it would have been obvious to substitute the Warnick nitric oxide detector for the Eads sulfur dioxide detector in the Eads system." *Id.* However, the Federal Circuit noted that "[t]here is no suggestion in Eads, which focuses on the unique difficulties inherent in the measurement of sulfur, to use that arrangement to detect nitrogen compounds." *Id.* The court determined that Eads actually taught away from the claimed invention because it said that the presence of nitrogen in the sulfur sample would be undesirable. *Id.* Thus, the court held that the finding of obviousness in this combination of references was based on impermissible hindsight, and that "[t]he Eads and Warnick references disclose, at most, that one skilled in the art might find it obvious to try the claimed invention. But whether a particular combination might be 'obvious to try' is not a legitimate test of patentability." *Id.* at 1075 (citations omitted).

The court also determined that the teachings of Warnick "are inconsistent with the claimed invention, to some extent," because Warnick measured nitric oxide in unseparated mixtures, whereas the claimed invention measured each nitrogen compound

separately. *Id.* at 1074-75. Thus, the court determined that "[t]he claimed system, therefore, diverges from Warnick and teaches advantages not appreciated or contemplated by it," and concluded that, "[b]ecause neither Warnick nor Eads, alone or in combination, suggests the claimed invention, the Board erred in affirming the Examiner's conclusion that it would have been obvious to substitute the Warnick nitric oxide detector for the Eads sulfur dioxide detector in the Eads system." *Id.* at 1075.

Analogous to *Fine*, the present invention diverges from Waterhouse and teaches advantages not appreciated or contemplated by it. Namely, the present invention allows direct expression and selection of polynucleotides encoding antigen-specific immunoglobulins by introducing two separate vaccinia virus expression libraries of heavy and light chains into mammalian host cells. The distinct and important advantages of performing immunoglobulin screening and selection in eukaryotic cells are discussed in detail in the Declaration of Dr. Maurice Zauderer ("Zauderer Declaration"), filed July 21, 2005. For example, the present invention provides the ability to screen for antibodies specific for membrane-associated proteins, which are isolated only with great difficulty from phage display libraries. Also, the present invention provides the ability to screen the expressed immunoglobulins for functionality (*e.g.*, effector functions associated with the constant region that is not included as part of the phage display fragment) as well as binding activity. The present invention further provides for eukaryotic post-translational modification and assembly that does not occur when antibody fragments are screened and selected by phage display. The lack of post-translational processing can affect binding and specificity of phage-selected antibodies when the fragments are removed from the phage fusion protein context. *See* Zauderer Declaration at pages 4, 7, and 8.

Furthermore, as discussed above and also analagous to *Fine*, when properly considering how Waterhouse would be viewed by one of ordinary skill in the art, it actually does teach away from the claimed invention because it emphasizes features that one of ordinary skill in the art would not have associated with eukaryotic expression systems (*e.g.*, ability to generate and screen large libraries and packing of heavy and light chains together in the same phage particle). As in *Fine*, the Examiner in the present case is using hindsight to suggest that it would have been obvious to one of ordinary skill to merely substitute the phage libraries of heavy and light chains in Waterhouse for the combination of a single heavy and light chain expressed from vaccinia virus vectors in Rowlands, and a single vaccinia virus library in Zauderer. This is an improper analysis under 35 U.S.C. § 103 and the Office has not established a *prima facie* case of obviousness.

3. Applicants' Arguments and Evidence are Commensurate in Scope With the Claims

The Office asserts that Applicants' arguments are not commensurate in scope with the claims. *See* Office Action at pages 22-23 and pages 38-40. In particular, the Examiner indicates that to the Storkus Declaration is beyond the scope of the claims because the claims do not require "'efficient' introduction of libraries into hosts [sic] cells, 'efficient' selection, libraries that are not 'poorly matched', the use of 'random pairs of immunoglobulins or the production of 'good' antibodies." *Id.* at page 22. Applicants respectfully submit that the Storkus Declaration is commensurate in scope with the claims in showing that one of ordinary skill in the art would not have had a reasonable expectation of success in combining Rowlands with Zauderer and Waterhouse to arrive at the present invention.

Dr. Storkus stated that he "thought specific antibodies of interest would occur at relatively low frequency and it would not be practical to screen the number of eukaryotic cells necessary in order to find an antibody that had specificity for a specific antigen of interest." Storkus Declaration at page 3. Furthermore, the fact that selection of antibody fragments had been performed in phage did not convince Dr. Storkus that eukaryotic cells could be used to screen for antigen-specific antibodies because of the limitations on screening throughput for eukaryotic cells compared to phage particles. Also, Dr. Storkus indicates that it was not clear, just because assembly of two separate immunoglobulin chain fragments in the periplasmic space of a prokaryotic cell could be achieved, that assembly in the cytoplasm of a eukaryotic cell would also occur to allow selection of polynucleotides encoding an antigen-specific immunoglobulin. *Id.* at pages 3-4.

Applicants, again, submit that the claims are directed to a method of selecting polynucleotides encoding an immunoglobulin heavy or light chain, which, as part of an immunoglobulin molecule, *is specific for an antigen*. If the immunoglobulin heavy and light chains are not capable of pairing together in the mammalian host cell--*e.g.*, if they do not "find" each other in the cytoplasm and assemble to form immunoglobulin molecules--then no antigen-specific immunoglobulin molecules could bind the antigen of interest or be detected as part of a specific antigen-antibody complex, and vaccinia virus vectors containing polynucleotides encoding the immunoglobulin subunit polypeptides could not be recovered according to the claimed method. This is completely commensurate in scope with the statements of Dr. Storkus.

The expectation of success is not shown to be reasonable by the disclosure of Rowlands because the Campath-1H heavy and light chains described in Rowlands were

already known to recognize antigen when paired together. This is qualitatively different than introducing *multiple* immunoglobulin heavy and light chains that must be capable of pairing to form immunoglobulin molecules *and* selecting polynucleotides encoding an antigen-specific immunoglobulin. *See, e.g.,* Storkus Declaration at page 5. Thus, Applicants respectfully submit that their support for showing that the Office has not established a *prima facie* showing of obviousness is commensurate in scope with the claims.

The Office also contends that the Zauderer Declaration is not commensurate in scope with the claims. Office Action at pages 34-35. In particular, the Examiner asserts that "the claimed invention is not limited to an 'efficient' method for the production of 'useful' antibodies. Thus, there was not a long felt need to produce antibodies (or fragments thereof) with low binding affinity and/or specificity as these goals were readily obtainable by other means"" *Id.* Applicants disagree with the Office's characterization of the statements made by Dr. Zauderer.

Applicants respectfully submit that the Office is basing its assessment of long-felt need on its improper distillation of the "gist" of the invention (*i.e.*, a method of producing an antibody), rather than considering the evidence of the Zauderer Declaration in assessing a long-felt need with respect to the *claimed invention*. The claims are directed to a method of selecting polynucleotides encoding an *antigen-specific human immunoglobulin molecule*. Full immunoglobulins produced, for example, from fragments selected by phage display that no longer recognize target antigen once they are removed from the phage context are not antigen-specific. *See* Zauderer Declaration at page 7. Furthermore, antibodies produced in prokaryotic cells are not processed or

assembled in the same manner as antibodies expressed in eukaryotic (*e.g.*, mammalian) cells, and therefore may lose antigen specificity due to improper folding. *Id.* at pages 4-5. As evidenced by Exhibits A2 and B2-B4 and as discussed in greater detail, below, the advantages offered by the present invention were desired by those in the art. Thus, Applicants respectfully submit that the Zauderer Declaration and the Exhibits of record are commensurate in scope with the claimed invention in showing a long-felt need.

4. Applicants' Objective Evidence of Nonobviousness Has Not Been Properly Considered by the Office

The Office asserts that Applicants' objective evidence of nonobviousness is insufficient to rebut a *prima facie* showing of obviousness. *See* Office Action at pages 31-34 and pages 40-42. Applicants disagree.

Applicants first would like to emphasize that the Office has not established a *prima facie* case of obviousness, as discussed in detail, *supra*, and in Applicants' previous replies. Applicants have provided evidence that there was a long-felt need in the art for a method of selecting polynucleotides which encode an antigen-specific human immunoglobulin molecule from eukaryotic, *e.g.*, mammalian, host cells according to the claimed invention as additional objective evidence of nonobviousness of the claimed invention. Applicants respectfully submit that this evidence has not been properly considered by the Office.

To the extent that the Examiner has repeated arguments made in the Office Action dated November 2, 2005, Applicants refer the Office to their Reply filed on February 2, 2006, which has been incorporated herein by reference in its entirety, and which Applicants believe to be fully responsive to the arguments in the present Office

Action. Nevertheless, Applicants also provide the following remarks to address additional comments presented in the present Office Action.

Specifically, the Examiner asserts that the evidence presented in Applicants Exhibits A2 and B2-B4, filed with Applicants Reply filed July 21, 2005, is deficient for a showing of long-felt need in the art. Office Action at page 33 and pages 40-41. With respect to Exhibit A2, the Examiner asserts that one quotation cited by Applicants, showing that one interviewee was still evaluating MAb companies, "doesn't state what the MAb companies are being evaluated for" and that "the passage doesn't even state that they picked Applicants' technology." Office Action at page 33. Applicants respectfully submit that the quotation from Exhibit A2, as well as the rest of the document, represents a survey indicating that, as of 2001, the existing antibody selection technologies (*e.g.*, phage display and transgenic mice) were not satisfactory to those of skill in the art who were looking for antibody selection platforms that could be used to identify antigen-specific antibodies, including antibodies to targets that would not elicit an immune response in a transgenic mouse and antibodies that could also be used in functional assays without having to reclone fragments isolated, *e.g.*, by phage display, into a full antibody structure. *See* Exhibit A2 at page 34.

Exhibits B2-B4 provide evidence that the claimed methods are recognized in the art as meeting the needs of these representative companies in the area of antibody discovery. The Examiner asserts that OPi's statements in Exhibit B2 are deficient because "OPi's statement doesn't even refer to any of the claimed features such as the use of a vaccinia virus eukaryotic expression system." However, Exhibit B4 does specifically indicate that the library-based technology is in vaccina vectors. *See* Exhibit

B4, last paragraph. The Examiner also asserts that the Exhibits are deficient because "the failure to solve a long-felt need may be due to factors such as a lack of interest or lack of appreciation of an invention's potential or marketability rather than want of technical know-how." Office Action at page 34 (citations omitted). Applicants point to Exhibit A2, which shows that those of ordinary skill in the art were interested in a technology with the features of the claimed invention.

At pages 40-41 of the Office Action, the Examiner asserts that Exhibits B2-B4 are insufficient rebuttal evidence because they do not show a nexus between the claimed invention and the strategic alliances based on use of the technology. In particular, the points to the specific language of Exhibit B4 and asserts that Applicants' claims are not limited to "bivalent, monoclonal fully human antibodies." Applicants claims are directed to a method of selecting polynucleotides that encode an antigen-specific *human immunoglobulin molecule*. The specification as filed defines "immunoglobulin molecule" as "a complete, bi-molecular immunoglobulin, *i.e.*, generally comprising four 'subunit polypeptides, *'i.e.*, two identical heavy chains and two identical light chains." Specification at Paragraph 0057.

The Examiner asserts that "while no details of the strategic alliances are given, it may very well be, for example, that the competitors decided, for business and/or financial reasons, not to pursue other opportunities. The decision not to pursue one opportunity as opposed to another may be dictated by many factors other than a need for the claimed features of Applicants' invention." Office Action at page 42. In response, Applicants point to Exhibit B2, in which OPi's CEO states that "Vaccinex's *innovative antibody discovery technology* will enable us to make a *technological leap* to develop

new fully human antibodies aiming at treating haematological diseases." Exhibit B2, 3rd Paragraph (emphasis added). To the extent that the Examiner asserts that the claims are not limited to haematological diseases, *see* Office Action at page 40, Applicants respectfully reiterate that, while each of the representative business organizations in Exhibits B2-B4 has, at a certain level of specificity, its own uses for the claimed invention (*e.g.*, developing antibodies to its own antigenic targets of interest), the diversity of uses for the claimed invention *among* various companies is evidence that the claimed invention has broader applicability than any of the single uses of any one company. Therefore, Applicants respectfully submit that the Exhibits of record provide evidence of a long-felt need for the methods of the present invention.

5. Summary

The Office has failed to establish a prima facie showing of obviousness because, in light of the foregoing reasons, one of ordinary skill in the art would not have been motivated to combine Rowlands with Zauderer and Waterhouse and would not have had a reasonable expectation of success. There was no teaching or suggestion in any of the cited references that the methods in each of the references could be used together. Furthermore, one of ordinary skill in the art would not expect that because Waterhouse *et al.* had developed a method of screening antibody fragments from a library of heavy chains and a library of light chains expressed in phage particles that the same thing could be done with vaccinia viruses in eukaryotic cells. This is so despite the fact that Rowlands describes how to express a single antibody heavy chain and a single antibody light chain from vaccinia viruses in mammalian cells, and despite the fact that Zauderer describes how to express one vaccinia virus library in mammalian cells. The fact that

there is overlap in some of the features of these references is not sufficient to show that one of ordinary skill in the art would have been motivated to combine them or would have had a reasonable expectation of success. It is only through distilling the invention down to its "gist" and the impermissible use of hindsight that the claimed invention can be pieced together by plucking selective elements from the references rather than considering each reference as a whole. Therefore, the requisite showing for a *prima facie* case of obviousness has not been made.

Furthermore, the cited references do not teach or suggest every element of the claimed invention because they do not describe the introduction of two vaccinia virus expression libraries into mammalian host cells for the selection of polynucleotides encoding immunoglobulin chains. As such, the Office has not met the requirements to establish a *prima facie* showing of obviousness.

In addition, Applicants have provided evidence of a long-felt need in the art for the claimed invention because the methods most commonly used before the present invention suffer from drawbacks and limitations that are overcome by the claimed method.

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be reconsidered and withdrawn.

B. Rejections for Obviousness-Type Double Patenting

At pages 42-47 of the Office Action, the Examiner has provisionally rejected claims 84, 88-97, 99, 103, 107-122, and 127-131, for alleged obviousness-type double patenting over claims 1-84 of commonly-owned U.S. Patent Application Publication No. 2003/0104402 A1 ("the '402 publication") in view of Rowlands. Applicants respectfully

traverse this rejection, and contend that claims 84, 88-97, 99, 103, 107-122, and 127-131 would not have been obvious to one of ordinary skill in the art over claims 1-84 of the '402 Publication in view of Rowlands.

One of ordinary skill in the art would not have had a reasonable expectation of success in combining Rowlands with the '402 publication to arrive at the present invention. Rowlands describes the use of vaccinia virus vectors for making an *individual* recombinant antibody, not an immunoglobulin expression library. There would have been no indication to one of ordinary skill in the art that the methods for making or screening a library of intracellularly expressed immunoglobulins, as described in the '402 publication could be used to make or screen a library of extracellularly expressed immunoglobulins as in the present invention based on the disclosure in Rowlands of an *individual antibody* that is expressed extracellularly. The Examiner is improperly focusing on the obviousness of differences and substitutions in making this rejection rather than on the invention as a whole. *See Hybritech*, 802 F.2d at 1383. Selection of previously unknown polynucleotides from the intracellular expression of two libraries of immunoglobulin heavy and light chains as disclosed in the '402 application is different than the expression of a single, previously selected antibody that is secreted into the culture medium as in Rowlands. Applicants respectfully submit that, as with respect to making a *prima facie* case of obviousness under 35 U.S.C. Section 103, it is improper "to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.'" *In re Hedges*, 783 F.2d 1038, 1041, 228 U.S.P.Q. 685 (Fed. Cir. 1986) (quoting *In re Wesslau*, 353 F.2d 238,

241 147, U.S.P.Q. 391, 393 (CCPA 1965)). Reconsideration and withdrawal of the rejection therefore are respectfully requested.

However, if the Examiner is not inclined to withdraw the rejection, then Applicants respectfully request that it be held in abeyance until such time as otherwise patentable subject matter has been identified in either the present application or the '402 publication. At that time, Applicants will consider filing a terminal disclaimer to obviate the double-patenting rejection.

At pages 48-57 of the Office Action, the Examiner has raised a new provisional rejection of claims 84, 88-97, 99, 103, 107-122, and 127-131, for alleged obviousness-type double patenting over claims 46-128 of commonly-owned U.S. Patent Application Publication No. 10/465,808 ("the '808 application") in view of Rowlands and Zauderer. Applicants respectfully request that this rejection be held in abeyance until otherwise allowable claims are identified, at which time Applicants will consider filing a Terminal Disclaimer.

C. Objections to the Claims

The Examiner has objected to claim 90 because the word "virions" was misspelled. Applicants thank the Examiner for pointing out the spelling error and have amended claim 90 to reflect the proper spelling. Therefore, Applicants respectfully request that this objection be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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